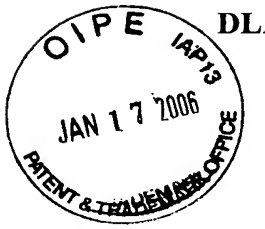
IPW



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DOCKET NO.: 3840-005-27

ASSISTANT COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA, VA 22313-1450

Re: Serial No.: 10/725,013
Applicant(s): Lakshman R. SEHGAL, et al.
Filing Date: December 2, 2003
For: EX VIVO AND IN VIVO EXPRESSION OF THE THROMBOMODULIN GENE FOR THE TREATMENT OF CARDIOVASCULAR AND PERIPHERAL VASCULAR DISEASES
Group Art Unit: 1635
Examiner: Brian A. Whiteman

SIR:

Attached hereto for filing are the following papers:

Preliminary Amendment and Response to Restriction Requirement
Copy of Date-Stamped Filing Receipt

Our check in the amount of $0.00 is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R. 1.136 for any necessary extension of time to make the filing of the attached documents timely, please charge or credit the difference to Deposit Account No. 50-1442. Further, if these papers are not considered timely filed, then a request is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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DOCKET NO. 3840-005-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Lakshman R. SEHGAL, et al. ART UNIT: 1635

SERIAL NO.: 10/725,013 EXAMINER: Brian A. Whiteman

FILING DATE: December 2, 2003

FOR: EX VIVO AND IN VIVO EXPRESSION OF THE THROMBOMODULIN GENE FOR THE TREATMENT OF CARDIOVASCULAR AND PERIPHERAL VASCULAR DISEASES

PRELIMINARY AMENDMENT
AND
RESPONSE TO RESTRICTION REQUIREMENT

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SIR:

Responsive to the Office Action dated November 10, 2005 and the Office communication dated December 27, 2005, Applicants elect, with traverse, Group I, Claims 1-13, the species of unmodified hemoglobin and the species of L-glutamine for further prosecution at this time.

Kindly amend the application as indicated below.

1. (Original) A method for treating a vascular disease in a mammal, wherein said method comprising the steps of:

infecting a segment of a blood vessel *in vitro* using a gutless adenoviral vector comprising a polynucleotide encoding a thrombomodulin protein or its variant;

grafting the virus-treated blood vessel in said mammal,

wherein said thrombomodulin protein or its variant is expressed in said virus-treated blood vessel in a amount sufficient to reduce re-occlusion or intimal hyperplasia in the grafted blood vessel.

2. (Original) The method of Claim 1, wherein said thrombomodulin protein has the amino acid sequence of SEQ ID NO:2.

3. (Original) The method of Claim 1, wherein said gutless adenoviral vector further comprises a regulatory element operably linked to the DNA sequence.

4. (Original) The method of Claim 3, wherein the regulatory element is a constitutive promoter selected from a group consisting of CMV promoter and RSV promoter.

5. (Orignial) The method of Claim 1, wherein the expression of said polynucleotide encoding a thrombomodulin protein or its variant is under the control of an inducible system.

6. (Original) The method of Claim 1, wherein said gutless adenoviral vector is produced using a shuttle vector comprising a pBR322 replication origin, a selectable marker gene, an adenovirus left inverted terminal repeat, an adenovirus encapsidation signal, an intronic sequence, and an adenovirus left inverted terminal repeat.

7. (Original) The method of Claim 6, wherein said selectable marker gene is Kanamycin resistance gene.

8. (Currently Amended) The method of Claim 1, wherein said mammal is human.

9. (Original) The method of Claim 1, wherein said infecting step further comprises:

filling the blood vessel with a complete viral delivery system comprising of 1: 1 mixture of Ham's F12 medium and DMEM, an effective amount of the gutless adenovirus vector, and an acellular oxygen carrier; and

incubating the blood vessel with the complete viral delivery system for a desired period of time.

10. (Original) The method of Claim 9, wherein said acellular oxygen carrier is selected from the group consisting of unmodified hemoglobin, chemically modified hemoglobin and perfluorochemical emulsions.

11. (Original) The method of Claim 10, wherein said unmodified hemoglobin or chemically modified hemoglobin is used in the range of 3 g/dl to 10 g/dl.

12. (Original) The method of Claim 9, wherein the complete viral delivery system further comprises at least one of L-glutamine, sodium bicarbonate, or antibiotic-antimycotic.

13. (Original) The method of Claim 9, wherein the desired period of time is between 10 to 45 minutes.

14. (Original) A method for treating a vascular disease in a mammal, wherein said method comprising the steps of:

evacuating a clot from a blood vessel in said mammal;

isolating a segment of the blood vessel around the evacuation site; and

infecting the segment of blood vessel *in vivo* using a gutless adenoviral vector comprising a polynucleotide encoding a thrombomodulin protein or its variant;

wherein the thrombomodulin protein or its variant is expressed in a amount sufficient to reduce re-occlusion or intimal hyperplasia in the infected segment of the blood vessel.

15. (Original) The method of Claim 14, wherein the isolating step further comprises the steps of:

inserting a balloon catheter to the site of evacuation; and

inflating a proximal balloon and a distal balloons to isolate the vessel segment around the site of evacuation.

16. (Original) The method of Claim 14, wherein said infecting step further comprises the steps of:

filling the isolated vessel segment with a complete viral delivery system comprising of 1: 1 mixture of Ham's F12 medium and DMEM, an effective amount of the gutless adenovirus vector, and an acellular oxygen carrier; and

incubating the isolated vessel segment with the complete viral delivery system for a desired period of time.

17. (Original) The method of Claim 14, wherein said thrombomodulin protein has an amino acid sequence of SEQ ID NO:2.

18. (Original) The method of Claim 14, wherein said gutless adenoviral vector comprises a regulatory element operably linked to a DNA sequence encoding a thrombomodulin protein or a variant of the thrombomodulin protein.

19. (Original) The method of Claim 18, wherein said regulatory element is a constitutive promoter selected from a group consisting of CMV promoter and RSV promoter.

20. (Original) The method of Claim 14, wherein said polynucleotide encoding a thrombomodulin protein or its variant is under the control of an inducible system.

21. (Original) The method of Claim 14, wherein said gutless adenoviral vector is produced using a shuttle vector comprising a pBR322 replication origin, a selectable marker gene, an adenovirus left inverted terminal repeat, an adenovirus encapsidation signal, an intronic sequence, and an adenovirus left inverted terminal repeat.

22. (Original) The method of Claim 14, wherein said mammal is human.

23. (Original) A method for treating a vascular disease in a mammal comprising administering a therapeutically effective amount of a gutless adenovirus vector into a segment of a blood vessel using a stent, wherein said gutless adenovirus vector is capable of expressing a thrombomodulin protein or a variant of the thrombomodulin protein.

24. (Original) The method of Claim 23, wherein said thrombomodulin protein has an amino acid sequence of SEQ ID NO:2.

25. (Original) The method of Claim 23, wherein said gutless adenovirus vector is embedded in said stent and is released only at a treatment site.

26. (Orignial) A composition for treating a vascular disease, comprising:

a gutless adenovirus capable of expressing thrombomodulin protein or a variant of the thrombomodulin protein, said gutless adenovirus is produced using a shuttle vector comprising a pBR322 replication origin, a selectable marker gene, an adenovirus left inverted terminal repeat, an adenovirus encapsidation signal, an intronic sequence, and an adenovirus right inverted terminal repeat.

27. (Original) A pharmaceutical composition for treating a vascular disease according to Claim 26, further comprising a pharmaceutically acceptable carrier.

28. (New) The method of Claim 1, wherein said infecting step further comprises:

filling the blood vessel with a complete viral delivery system comprising a 1: 1 mixture of Ham's F12 medium and DMEM, an effective amount of the gutless adenovirus vector, an acellular oxygen carrier; and at least one of L-glutamine, sodium bicarbonate, or antibiotic-antimycotic; and

incubating the blood vessel with the complete viral delivery system for a desired period of time.

29. (New) The method of Claim 28, wherein the complete viral delivery system comprises the 1: 1 mixture of Ham's F12 medium and DMEM, the effective amount of the gutless adenovirus vector, the acellular oxygen carrier; and L-glutamine.

30. (New) The method of Claim 9, wherein said acellular oxygen carrier is unmodified hemoglobin.

31. (New) The method of Claim 30, wherein said unmodified hemoglobin is present in an amount of 3 g/dl to 10 g/dl.

32. (New) The method of Claim 28, wherein the desired period of time is between 10 to 45 minutes.